PHOTOALLERGY AND PRIMARY PHOTOSENSITIVITY TO SULFANILAMIDE[1]

STEPHAN EPSTEIN, M.D.

Marshfield Clinic, Marshfield, Wis.

(Received for publication August 22, 1938)

Hypersensitivity to light presents many unsolved problems. Sulfanilamide, as a photosensitizing drug (1–7), seemed suitable for a study of the mechanism of this sensitivity. The following is a report on experimental cutaneous sensitization with sulfanilamide and light, which revealed two different types of skin reactions.

TECHNIC

The experiments were carried out on 5 volunteers and myself.

0.1 cc. of a 1% solution of sulfanilamide (Squibb), in physiologic saline solution, was injected intradermally. Controls were made with injections of the saline solution alone.

The injections were followed by an irradiation always within 24 hours, and in most instances after 15 to 45 minutes.

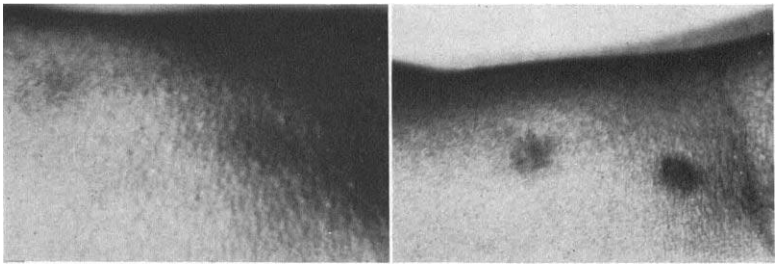
As a rule the irradiation was given with an air-cooled quartz lamp; in some few instances the Kromayer lamp or natural sunlight were applied.

RESULTS OF EXPERIMENTS

A. Primary photosensitivity (photodynamic action)

Sulfanilamide produces a primary photosensitivity of the site of intracutaneous injection. This is demonstrated by the fact that the injection of sulfanilamide followed by an erythema dose of ultraviolet rays produced in all (22) experiments an erythematous reaction of about 0.8 to 1.0 cm. in diameter, contrasting with the milder erythema of the surrounding skin. (Figs. 1a and 3a). This reaction appeared after 1 to 24 hours, persisted for several days and led eventually to pigmentation (Fig. 1b).

[1] I wish to express my thanks to Dr. R. P. Potter for his assistance in the preparation of this paper.



a b

FIG. 1. PRIMARY PHOTOSENSITIVITY PRODUCED BY SULFANILAMIDE (QUARTZ LAMP)

(a) Erythema, appearing 3 hours after irradiation, lasting 4 days. (Photo on fourth day.)

(b) Same case. Pigmentation following erythema. (Photo on eleventh day.)

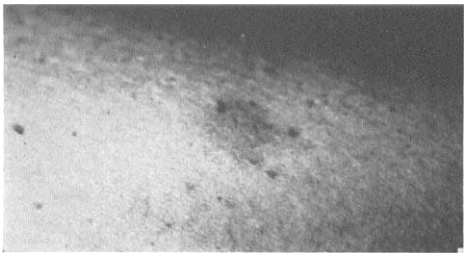
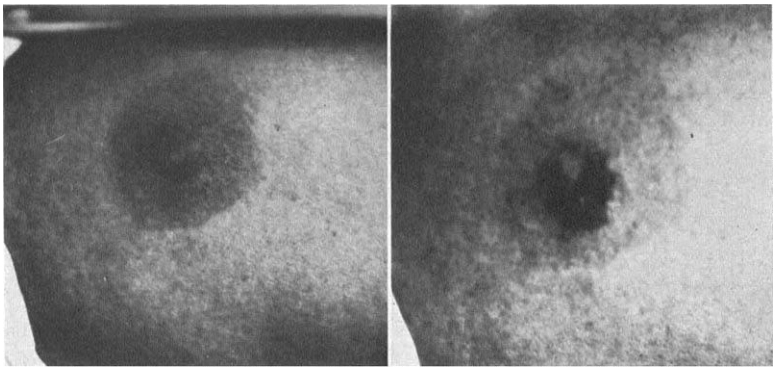


FIG. 2. PRIMARY PHOTOSENSITIVITY PRODUCED BY SULFANILAMIDE (SUN LIGHT)

Erythema, appearing after 2 hours. (Photo on first day.)



a b

FIG. 3a. Primary photosensitivity produced by sulfanilamide; (3b) spontaneous appearance of photo*allergic* reaction at the same site 10 days later.

(a) Kidney-shaped primary erythema, contrasting with surrounding pigmentation (Kromayer lamp). (Photo on fourth day.)

(b) *Allergic*, infiltrated, inflammatory-urticarial reaction, appearing on 10th day. Note similarity to configuration of primary reaction. (Photo on eleventh day.)

B. Allergic photosensitivity (photoallergy)

A different type of reaction appeared in 2 of the test persons on the 10th day. At this time an inflammatory, urticarial reaction, with intense pruritus developed spontaneously at the site of the primary reaction. This later reaction was considerably larger than the original response, but of similar configuration (Fig. 3b). It persisted for 10 to 14 days. This reaction which appeared on the 10th day was quite obviously entirely different from the primary one. Every subsequent experiment in the two sensitized persons produced a reaction of the type of the later spontaneous inflammatory-urticarial response, but now appearing not 10 days but 10–24 hours after the performance of the test.

A comparison and details of both types of reaction are given in table 1.

DISCUSSION AND CONCLUSIONS

These experiments demonstrate a true allergic type of photosensitivity (photoallergy). As far as I can see, this is the first report of this particular type of photosensitization and the first experimental proof of the allergic nature of this form of light sensitivity.[2] Certainly more experimental work will be necessary to clarify the relationship of this form of response to various forms of clinical hypersensitivity to light. The possibility of other manifestations and different mechanisms in photoallergic reactions has to be considered. Therefore, I shall at present briefly discuss only a few points which may indicate this relationship.

MECHANISM OF THE PHOTOALLERGIC REACTION

The reaction fulfills the requirements of a true allergic phenomenon; the capacity to react is produced by a previous contact and is manifested, *after a definite incubation period* (in my cases, of 10 days), by an altered and accelerated reaction to a subsequent exposure to the same agents, namely sulfanilamide plus light (reaction in 10–24 hours).

[2] The so-called *urticarial light reaction* (9, 12–14), not identical with the above described type, is sometimes called "allergic"; but its allergic nature is not proven, although probable in some instances. It has not been demonstrated that certain clinical types of photosensitivity are in general based on specific acquired alterations in the capacity to react; and these forms cannot be termed allergic until this demonstration has been submitted.

TABLE I

Comparison of primary photosensitization and allergic sulfanilamide—light reaction

	PRIMARY REACTION (PHOTODYNAMIC REACTION)	ALLERGIC REACTION (PHOTOALLERGY)
1. Occurrence of reaction	In all (6) test persons, at the first exposure (22 experiments)	Only in 2 out of 6 test persons, after an interval of 10 days from the appearance of the first primary reaction; and in these two persons after each subsequent test (26 experiments)
2. Type of reaction		
a. Characteristics	Erythema of several days' duration followed by pigmentation (Figs. 1a and 1b)	Urticarial inflammatory reaction (Figs. 3b and 4), without apparent pigmentation, lasting for 10–14 days
	No swelling	Swelling and infiltration
	No wheal formation after rubbing	Wheal formation after rubbing
b. Size	0.8 to 1.0 cm. in diameter	1.5 to 4.0 cm. in diameter
c. Configuration	Round (Fig. 1a) or kidney-shaped (Fig. 3a)	At site of primary reaction similar to it in form (Figs. 3a and 3b). At new sites more or less round, with or without lymphangitic (?), finger-like spread
d. Subjective symptoms	None	Intense pruritus
e. Comparison with ordinary ultraviolet erythema	Only quantitative differences	Entirely different
3. Conditions of reaction		
a. Amount of sulfanilamide	Increased reaction with increase of dose. Larger amount necessary for primary reaction. 0.01 cc. not effective	Increased reaction with increase of dose. 0.01 cc. effective
b. Amount of ultraviolet	Degree of reaction increased with dosage (to some extent)	Degree of reaction increased with dosage
Quartz lamp	At least mild erythema dose necessary	Suberythema doses sufficient. ½ of the amount necessary for a primary reaction effective
Natural sun light	Appeared, more effective than quartz lamp	Natural sunlight more effective. Reaction produced even by diffuse light on a hazy day
c. Time interval between injection and irradiation. The latter had to follow	Within at least 3 to 4 hours	Within at least 6 to 8 hours
d. Injection of sulfanilamide irradiated in vitro (with or without human serum)	Not effective	Not effective
e. Irradiation of skin previous to injection	Not effective	Not effective
f. Effect of ultraviolet without injection	No abnormal reaction	No abnormal reaction
g. Effect of sulfanilamide without light (injection and patch test)	Not effective (24 experiments)	Not effective (19 experiments), except in 2 out of 10 instances where sulfanilamide was injected, simultaneously with irradiation of another site (see page 43)
4. Influence of previous reactions on further injections		
a. Local reinjection	Apparently not different	Shortening of incubation period, peak and duration of reaction
b. General effect	Apparently always same under same circumstances	Change in allergic state apparent. Degree of hypersensitivity decreasing after 2 months, but previous level reattained and exceeded by subsequent experiments
5. Passive transfer		Inconclusive

The following hypothesis may be advanced for the understanding of the mechanism of the reaction: The irradiation of sul-

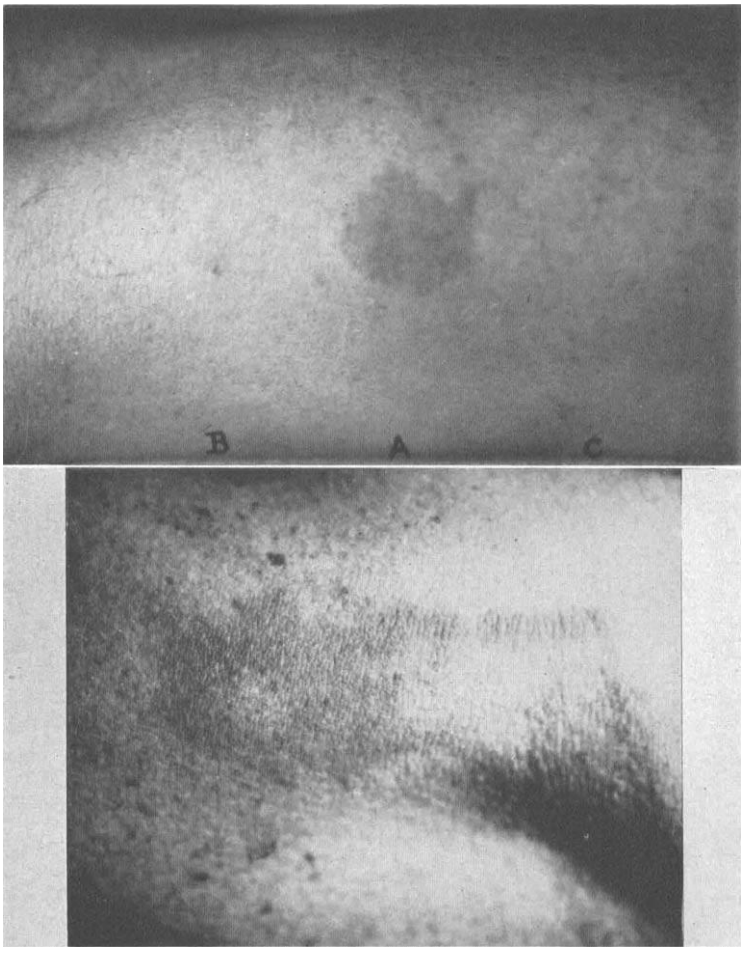


FIG. 4. ALLERGIC LIGHT REACTIONS PRODUCED BY SULFANILAMIDE
(a) Produced by quartz lamp. A: Reaction at site of sulfanilamide + ultraviolet irradiation. B: No reaction at site of sulfanilamide without light (control). C: No reaction at site of saline solution + ultraviolet (control).
(b) Produced by sun light.
Note lymphangitic extension at right side, ending with irradiated area.

fanilamide in the skin produces a substance responsible for the appearance of the primary reaction. Following this reaction,

the skin of certain predisposed individuals becomes sensitized to this substance (2 of 6 subjects in my experiment). A similar possibility has been suggested in connection with physical allergy, first by J. Jadassohn (8–11a).

This hypothesis could explain nearly all the clinical and experimental observations.

The fact that sulfanilamide irradiated in vitro did not produce a reaction, does not necessarily speak against the expressed hypothesis. Experiments with an extract from an irradiated site were not performed.

The occasional "flare-up" of a site injected with sulfanilamide alone and without irradiation (see table 1, column 3 g) cannot be explained without further assumptions. This question deserves more study as it may bear some relation to those clinical observations in light sensitization diseases where lesions were found on covered areas, as reported in sulfanilamide (3), acridin (15, 16), and other photodermatoses (17–19). The complexity of the problem is indicated by the following observation: The site of a previous sulfanilamide injection (without irradiation) in a sensitized person, showed a different behavior to subsequent reinjection plus irradiation, in comparison to normal skin. The reaction apparently took a shortened course although not so pronounced as in the case of a previously reacting site (see table 1, column 4a).

CORRELATION OF EXPERIMENTAL RESULTS WITH CLINICAL OBSERVATIONS

From a clinical point of view one may distinguish the following pathological light reactions (excluding the ordinary traumatic effects):

I. The light as essential noxa (18), or specific factor (19).
   a. primary photosensitivity (photodynamic action).
   b. photoallergy.

II. The light as incidental (or synergistic) factor (18):
   a. non-specific provocation through light.

I. (a) Primary photosensitivity produced by sulfanilamide.

A primary photosensitivity is suggested in several cases of sulfanilamide eruptions (5). I recall two instances of a severe reaction to light among patients treated for erysipelas with sulfanilamide combined with ultraviolet irradiations.[3] It may be

[3] It seems advisable that in combining both methods, the administration of sulfanilamide should follow rather than precede the irradiation. After using this procedure, I have not seen any abnormal reaction.

mentioned that the photosensitivity due to acridin derivates (20, 21) usually manifests itself as excessive sunburn. There is a difference between the experimental primary photosensitivity which could be demonstrated in all tested persons, and the corresponding clinical observations which occur only in a certain percentage of the exposed persons (with sulfanilamide as well as with acridin derivates). This difference may be partly explained by quantitative factors, for it has been shown that a certain minimum amount of the drug and ultraviolet rays is necessary to elicit the reaction of primary photosensitization. Furthermore, as the picture of primary photosensitivity differs only in degree from that of an ordinary sunburn, cases may have been overlooked, or could not be differentiated from ordinary effects of ultraviolet.

I. (b) Photoallergy to sulfanilamide

An allergic light reaction seems to be present in other reports of sulfanilamide eruptions (2–5). This is especially evident in those cases with negative skin tests to sulfanilamide alone.

II. (a) Non-specific provocation of sulfanilamide dermatitis

This mechanism is assumed in some other cases in the literature (7). Only further study and thorough analysis of those and analogous cases can show whether we have to deal with photoallergy or non-specific provocation.

APPLICATION OF THE PHOTOALLERGIC PRINCIPLE TO OTHER LIGHT DERMATOSES

The photoallergic phenomenon may play a rôle in and may help to understand the mechanism of other diseases due to light, for example urticaria photogenica, eczema solare, summer prurigo and allied conditions, ("actino-anaphylactoses") (22), phagopyrism (from buckwheat), etc. In this connection I shall mention only a few of the numerous reports suggesting a combined action of light and allergy (8, 11, 17, 22–28). The relationship between exposure to light and the manifestations of dermatoses like lupus erythematosus, erythema multiforme, etc. also might be studied in regard to the possibility of photoallergic mecha-

nisms. In this connection it is well to bear in mind the photosensitizing effects of microbic and metabolic products (17, 29–31).

SUMMARY

1. A primary cutaneous photosensitivity and an allergic light reaction (photoallergy) were produced by intracutaneous injections of sulfanilamide.

2. The allergic nature of this second, newly described form of photosensitivity is demonstrated.

3. The characteristics and distinguishing features of these two different photosensitizing effects are described and discussed.

4. The possible mechanisms and the clinical significances of these two forms of reaction to light are discussed.

BIBLIOGRAPHY

(1) NEWMANN, BEN A. AND SHARLIT, HERMAN: Sulfanilamide: A photosensitizing agent of the skin. J. A. M. A., **109**: 1036–1037, 1937.

(2) EPSTEIN, STEPHAN: Discussion to Tedder (7), 225–226.

(3) FRANK, LOUIS J.: Dermatitis from Sulfanilamide. J. A. M. A., **109**: 1011–1012, 1937.

(4) MENWILLE, JOHN G. AND ARCHINARD, JOHN J.: Skin eruptions in patients receiving sulfanilamide. J. A. M. A., **109**: 1008–1009, 1937.

(5) BRUNSTING, L. A.: Sulfanilamide Dermatitis: Question of Relation to Photosensitivity. Proc. Staff Meet. Mayo Clin., **12**: 614, 1937.

(6) SULZBERGER, MARION B. AND GOODMAN, JOSEPH: Allergy in Dermatology: A critical review of recent contributions. J. Allergy, **9**: 398–423, 1938.

(7) TEDDER, J. W.: Toxic manifestations in the skin following sulfanilamide therapy. Eighty-ninth Annual Session of the A. M. A. San Francisco, Cal., June 13–17, 1938. Arch. Dermat. & Syph., **39**: 217–227, 1939.

(8) BERNSTEIN, FRITZ: (a) Zum allergischen Character der Kälteurticaria. Dermat. Zeitschr., **64**: 242–246, 1932. (b) Beitraege zu den physikalischen Idiosynkrasien der Haut. IV. Mitteilung. Spezifische Sensibilisierung als Ursache idiosynkrasischer Lichtdermatosen. Arch. f. Dermat. u. Syph., **168**: 177–182, 1933.

(9) DUKE, W. W.: (a) Urticaria caused by light. J. A. M. A., **80**: 1835–1838, 1923. (b) Physical allergy as a cause of dermatoses. Arch. Dermat. & Syph., **13**: 176–186, 1926.

(10) JADASSOHN, J.: Die Toxicodermien. Die Deutsche Klinik am Eingange des zwanzigsten Jahrhunderts., **10**: 2, Dermatologie, pg. 117–153. Urban und Schwarzenberg. Berlin—Wien. 1905. (pg. 119–120 (footnote).)

(11) ROWE, ALBERT H.: Clinical Allergy. Lea and Febiger. Philadelphia, 1937 (p. 393).

(11a) SELLEI, JOSEPH: Beiträge zu den physikalischen Allergien. Arch. f. Dermat. u. Syph., **161**: 32–42, 1930.

(12) Blum, H. F. and West, R. J.: Studies of an urticarial response to blue and violet light in man. J. Clin. Investigation, **16:** 261–277, 1937.
(13) Frei, W.: Versuche zur urticariellen Lichtreaktion. Arch. f. Dermat. u. Syph., **151:** 66, 1926.
(14) Wucherpfennig, V.: Pathologische Lichtüberempfindlichkeit in qualitativer und quantitativer Hinsicht. Arch. f. Dermat. u. Syph., **156:** 520, 1928.
(15) Jausion and Marceron, quoted from Hausmann and Haxthausen (17).
(16) Oppenheim, M., quoted from Hausmann and Haxthausen (17).
(17) Hausmann, W. and Haxthausen, H.: Die Lichterkrankungen der Haut. Sonderbaende zur Strahlentherapie, vol. 9. Urban & Schwarzenberg. Berlin-Wien, 1929.
(18) Rost, G. A. and Keller, Philipp: Die Wirkungen des Lichtes auf die gesunde und kranke Haut. Handbuch der Haut- und Geschlechtskrankheiten (Jadassohn), **5:** II, 1–162. Julius Springer, Berlin, 1930.
(19) Senear, Francis Eugene and Fink, Harry W.: Hydroa vacciniforme seu aestivale. Arch. Dermat & Syph., **7:** 145–161, 1923.
(20) Ambrogio, Agostino: Indagini sperimentali sopra i fenomeni di sensibilizzazione fotodinamica in dermatologia, etc. Arch. ital. di dermat., sif., **12:** 602–627 (1936).
(21) Mayer, R. L.: Toxicodermien I. Handbuch der Haut- und Geschlechtskrankheiten (Jadassohn), **4:** II, 1–252. Julius Springer, Berlin, 1933.
(22) Jausion, Hubert and Pagès, François: Les maladies de lumière et leur traitement. Chapter 9: Les actino-anaphylactoses, pg. 122–174. Masson et Cie, Paris, 1933.
(23) Glaubersohn, S. A. and Goldenberg, M. M.: Zur Lehre über die Photodermatosen. Dermat. Wchnschr., 1930, II, 1625–1632.
(24) Mühlmann, J. and Akobjan, A.: Experimenteller Beitrag zur Aetiologie der Prurigo aestivalis. Arch. f. Dermat. u. Syph., **159:** 318–323, 1930.
(25) Cummer, Clyde L. and Dexter, Richard: Dermatitis caused by Dictamnus albus (Gas plant). J. A. M. A., **109:** 495–497, 1937.
(26) Hill, L. W., quoted from Rowe (11), pg. 393.
(26a) Juon, M.: Strahlenüberempfindlichkeit nach generalisierter Dermatitis infolge einer Salvarsan- und Hg-Kur. Arch. f. Dermat. u. Syph., **156:** 355–366, 1928.
(27) Pagès, François: Les deux modalités principales de l'eczéma solaire: eczéma solaire vrai et eczéma photomicrobien. Bull. med., Paris. 1933, 217–218, abstract: Zentralbl. f. Haut- und Geschlechtskr. **45:** 215, 1933.
(28) Urbach, E.: Lichtdermatosen und Eiklar- und Eigelb-Ueberempfindlichkeit. Oesterr. Dermat. Ges. Wien, May 14, 1936. Zentralbl. f. Haut- u. Geschlechtskr., **55:** 181, 1937.
(29) Gross and Volk, quoted from Hausmann and Haxthausen (17).
(30) Sulzberger, M. B.: Discussion to Stokes and Callaway (31).
(31) Stokes, John H. and Callaway, J. Lamar: Pyogenic relapse and sensitiveness to light in certain dermatoses. Arch. Dermat. & Syph., **36:** 976–983, 1937.